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Preparation of azithromycin

Abstract:

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(54) Preparation of azithromycin

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EP 0 879 823 A1

Description

This invention relates to the preparation of azithromycin.

Azithromycin is a well-known semi-synthetic macrolide antibiotic (U.S. patent nos. 4,474,768 and 4,517,359). It is prepared through the expansion/inclusion of a nitrogen atom in the macrolide ring of erythromycin A, followed by reductive methylation. Azithromycin is more stable and more effective, particularly against gram-negative bacteria, than erythromycin A.

The reaction sequence to transform erythromycin A into azithromycin involves extremely strong and aggressive reaction conditions (J. Chem. Soc. Perkin Trans. I, 1881 (1986)), and requires the isolation of intermediates which, in certain conditions, are even more unstable than the starting material. Reaction conditions and isolation procedures must be mild and very strictly controlled. This can give problems when a laboratory scale process is put into practice on an industrial scale. Additional restrictions have to be included in the manufacturing process in order to ensure that the azithromycin is obtained in good yield and high purity.

The transformation of erythromycin A into azithromycin involves conversion of erythromycin into its oxime; Beckmann rearrangement of the oxime to the imino ether of erythromycin A; reduction of the imino ether to 9-deoxo-9a-aza-9a-homoerythromycin; and, finally, reductive N-methylation to obtain the azithromycin.

The reduction of the imino ether step and the reductive methylation step have so far been described in a two stage process (EP-A-0109253). This enables separation and purification of the intermediate 9-deoxo-9a-aza-9a-homoerythromycin before proceeding to the second stage. However, we have now appreciated that having a two stage process of this sort is undesirable and we have found that, surprisingly, it is not necessary and that significant advantages can be achieved by using a different procedure.

According to the present invention, it has been found that an imino ether of erythromycin can be reduced, and the product thus obtained can be subsequently submitted to reductive methylation in the presence of the same noble metal catalyst and in the presence of formaldehyde or a source thereof, without any isolation of the intermediate product. The two reactions already known *per se* can thus be conducted using the same catalytic system in the same reaction vessel and in the same reaction medium. By carefully choosing the reaction conditions, one can obtain a product of good purity and with a good yield. Thus, the present process represents a considerable industrial advantage over the prior art by reducing the number of reactors and manipulations, like the isolation of the intermediate product.

The invention thus provides a process for the preparation of azithromycin from an imino ether, which process comprises reduction and reductive methylation of said imino ether carried out sequentially with a noble metal catalyst and hydrogen in the presence of formaldehyde, or a source thereof, and wherein both reactions are conducted in the same reaction vessel.

According to published literature, the conditions which have been found to be most effective for the reduction of the imino ether involve utilisation of reducing agents in stoichiometric amounts or high pressure hydrogenation using platinum (WO-A-94/26758). This is then followed by isolation of the cyclic amine, which is then subject to reductive methylation employing the well-known Eschweiler-Clarke conditions (formaldehyde and formic acid in chloroform) or by hydrogenation (formaldehyde and hydrogen in the presence of a noble metal catalyst) (U.S. patent no 4,517,359, J. Chem. Res., 1988, 1239-1261).

Reduction of the imino ether using sodium borohydride (EP-A-0109253, J. Chem Soc. Perkin Trans., I, 1986, 1881) involves an extremely exacting procedure as far as completion of the reaction and recovery of the product are concerned. The initial intermediate present in the reaction medium is apparently a boron containing complex, which must be destroyed in order that the desired 9-deoxo-9-a-aza-9a-homoerythromycin can be isolated. The complex in question must be eliminated under acid conditions and since, as is known, the macrolide is sensitive to acid media, the conditions for this step must be rigorously controlled. This procedure becomes even more difficult on an industrial scale, since the times of contact between the sensitive intermediate and the undesired aqueous acid medium are inevitably more prolonged.

In the present invention, these difficulties are reduced or completely overcome by synthesising the 9-deoxo-9a-aza-9a-homoerythromycin intermediate, preferably under mild conditions, so that it is not necessary for it to be isolated or purified prior to the following step. Naturally isolation of this intermediate can be effected, if so desired. The reduction is generally carried out at a temperature between 0-50°C, the preferred range being between 20-25°C. At these temperatures, side reactions such as hydrolysis of the glycosides present in the molecule are reduced, especially hydrolysis involving the cladinose unit.

The process of the invention can be conducted in any suitable organic solvent. The preferred solvent is acetic acid, containing different percentages of water. Other organic solvents, such as ethanol, tetrahydrofuran, dioxane or mixtures thereof with water, can also be used.

Pressures which lead to the best results and to acceptable reaction times are those between 20-70 bar, but other pressures outside these limits can also be used.

The preferred reduction catalyst is 5% rhodium-on-carbon, although other noble metal catalysts, such as platinum, palladium or ruthenium, can also be used. The amount of rhodium used can vary but we prefer to use from 0.5 to 2% calculated with respect to the starting

material. The use of amounts outside this range can result in changes in reaction times which can be a disadvantage.

The formaldehyde is preferably provided as a 37% aqueous solution thereof or as para-formaldehyde, although other sources can be used. The amount of formaldehyde used is generally from 23 to 100 moles/mole of the imino ether. A further smaller amount of catalyst may be added so as to complete the reaction within a reasonable time.

If desired, the catalyst can be recycled and re-used several times, thus rendering the process more economic.

The azithromycin is isolated by adjusting the pH of the reaction mixture to between 9 and 10. In this manner, it is possible to obtain azithromycin of acceptable purity. Crystallization from a mixture of ethanol/water can yield a product with a sufficiently high purity for it to be used as starting material in the pharmaceutical industry.

The present invention affords, among others, the following advantages: namely two chemical reactions in only one reaction vessel; use of less sophisticated industrial equipment, given the fact that one of the intermediates is not isolated; and the use of milder reaction conditions, giving a pure product with a high yield.

The following non-limiting Examples illustrate the present invention.

EXAMPLE 1

To a solution of 2 g (2.7 mmoles) of the imino ether of erythromycin A, (prepared by the usual techniques) in 20 ml of acetic acid, there was added 0.03 g (0.38 mmoles) of sodium acetate and 0.5 g of wet 5% Rh/C (11.25 mg Rh). The mixture was then hydrogenated at a pressure of 70 bar and at 40°C for 3 hours. At the end of this period, 27 ml of an aqueous solution containing 37% formaldehyde (0.36 moles) was added under atmospheric pressure and at room temperature, and the mixture hydrogenated at 40 bar and at a temperature of 40°C for 20 hours. The catalyst was filtered off and the filtrate evaporated until an oil was obtained. To the oil so obtained, 45 ml of water was added, and the pH of the solution was adjusted to 9.3 with NaOH 4N. After stirring for 2 hours at room temperature, the solid was filtered, washed with water, and dried, yielding 1.2 g of crude azithromycin with a purity of 97% after recrystallization.

EXAMPLE 2

To a solution of 4 g (5.4 mmoles) of the imino ether of erythromycin A, (prepared by the usual techniques) in 20 ml of acetic acid, there was added 1 g of wet 5% Rh/C (22.5 mg Rh). The mixture was hydrogenated at 60 bar and at a temperature of 40°C for 5 hours. At the end of this period, 22.5 ml of an aqueous solution containing 37% formaldehyde (0.3 moles) was added under atmospheric pressure and at room temperature, and the mixture was then hydrogenated at 40 bar and at a temperature of 40°C for 20 hours. The catalyst was filtered off and the filtrate evaporated until an oil was obtained. To this oil, 90 ml of water was added, and the pH of the solution was adjusted to 9.4 with NaOH 4N. After stirring for 2 hours at room temperature, the solid was filtered, washed with water, and dried, yielding 2 g of crude azithromycin with a purity of 97% after recrystallization.

EXAMPLE 3

To a solution of 8 g (10.9 mmoles) of the imino ether of erythromycin A, (prepared by the usual techniques) in 32 ml of acetic acid and 8 ml of water, there was added 8 g of wet 5% Rh/C (180 mg Rh). The mixture was then hydrogenated at 70 bar and at room temperature for 2 hours. At the end of this period, 40 ml of an aqueous solution containing 37% formaldehyde (0.54 moles) was added, and the mixture was hydrogenated at 40 bar and at a temperature of 40-45°C for 20 hours. The catalyst was filtered off, and the pH of the filtrate was adjusted to 9.4 with NaOH 4N. After stirring for 2 hours at room temperature, the solid was filtered, washed with water, and dried, yielding 7 g of crude azithromycin with a purity of 95% after recrystallization.

EXAMPLE 4

To a solution of 4 g (5.4 mmoles) of the imino ether of erythromycin A, (prepared by the usual techniques) in 4 ml of acetic acid and 16 ml of water, there was added 4 g of wet 5% Rh/C (90 mg Rh). The mixture was hydrogenated at 70 bar and room temperature for 2 hours. At the end of this period, 25 ml of an aqueous solution containing 37% formaldehyde (0.34 moles) was added under atmospheric pressure at room temperature and the mixture was hydrogenated at 40 bar and at a temperature of 40-45°C for 24 hours. The catalyst was filtered off, and the pH of the filtrate adjusted to 9.4 with NaOH 4N. After stirring for 2 hours at room temperature, the precipitate was filtered off, washed with water, and dried, yielding 2.8 g of crude azithromycin with a purity of 98% after recrystallization.

EXAMPLE 5

To a solution of 8 g (10.9 mmoles) of the imino ether of erythromycin A, (prepared by the usual techniques) in 24 ml of acetic acid there was added 8 g of wet 5% Rh/C (180 mg Rh). The mixture was hydrogenated at 70 bar and at room temperature for 2 hours. At the end of this period, 50 ml of an aqueous solution containing 37% formaldehyde (0.67 moles) was added under atmospheric pressure at room temperature, and the mixture was hydrogenated at 40 bar and 40-45 °C for 24 hours. The catalyst was filtered off, and the pH of the filtrate was adjusted to 9.5 with NaOH 4N. After stirring

for 2 hours at room temperature, the solid was filtered, washed with water, and dried, yielding 6.1 g of crude azithromycin with a purity of 98% after recrystallization.

EXAMPLE 6

To a solution of 4 g (5.4 mmoles) of the imino ether of erythromycin A, (prepared by the usual techniques) in 18 ml of acetic acid and 2 ml of water, there was added 2 g of wet 5% Rh/C (45 mg Rh). The mixture was then hydrogenated at 70 bar and at room temperature for 2 hours. At the end of this period, 35 ml of an aqueous solution containing 37% formaldehyde (0.47 moles) was added under atmospheric pressure at room temperature, and the pH was adjusted to from 3 to 4 with NaOH 4N. The mixture was hydrogenated at 40 bar and at a temperature of 40-45 °C for 24 hours. The catalyst was filtered off, and the pH of the filtrate was adjusted to 9.4 with NaOH 4N. After stirring for 2 hours at room temperature, the solid was filtered, washed with water, and dried, yielding 2.7 g of crude azithromycin with a purity of 96% after recrystallization.

EXAMPLE 7

To a solution of 8 g (10.9 mmoles) of the imino ether of erythromycin A, (prepared by the usual techniques) in 8 ml of acetic acid and 32 ml of water, there was added 8 g of wet 5% Rh/C (180 mg Rh). The mixture was hydrogenated at 70 bar and at 40°C for 2 hours. At the end of this period, 10 g (0.33 moles) of para-formaldehyde was added under atmospheric pressure at room temperature, and the pH of the reaction mixture was adjusted to 4 with NaOH. Hydrogenation was carried out at a pressure of 40 bar and at a temperature of 40-45 °C for 24 hours. The catalyst was filtered off, and the pH of the reaction mixture was adjusted to 9.2 with NaOH 4N. After stirring for 2 hours at room temperature, the solid was filtered, washed with water, and dried, yielding 4.98 g of crude azithromycin with a purity of 97% after recrystallization.

Claims

1. A process for the preparation of azithromycin from an imino ether, which process comprises reduction and reductive methylation of said imino ether carried out sequentially with a noble metal catalyst and hydrogen in the presence of formaldehyde, or a source thereof, and wherein both reactions are conducted in the same reaction vessel.

2. A process according to claim 1, wherein the formaldehyde or a source thereof is added at the beginning of the reduction.

3. A process according to claim 1, wherein the formaldehyde or a source thereof is added at the beginning of the reductive methylation.

4. A process according to claim 1, 2 or 3, wherein the noble metal is Pd, Pt, Rh or Ru.

5. A process according to claim 1, 2, 3 or 4, wherein the formaldehyde is provided as formalin or a as para-formaldehyde.

6. A process according to any of claims 1 to 5, which is conducted in the presence of acetic acid or formic acid or another organic solvent.

7. A process according to claim 6, which is conducted in the presence of ethanol as organic solvent.

8. A process according to any of claims 1 to 7, wherein the acidity is controlled by use of a buffer.

9. A process according to claim 8, wherein the buffer is sodium acetate.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 98 30 3945

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
D,A	WO 94 26758 A (PFIZER ;YANG BINGWEI V (US)) 24 November 1994 * the whole document *	1	C07H17/08
D,A	US 4 517 359 A (KOBREHEL GABRIJELA ET AL) 14 May 1985 * the whole document *	1	

TECHNICAL FIELDS SEARCHED (Int.Cl.6)

C07H

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	24 July 1998	Scott, J

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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